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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOX ROTHSCHILD LLP PRINCETON PIKE CORPORATE CENTER 2000 Market Street Tenth Floor Philadelphia, PA 19103			EXAMINER STEELE, AMBER D	
			ART UNIT 1639	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/536,705	Applicant(s) MONTELIONE ET AL.	
	Examiner AMBER D. STEELE	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 94-116 is/are pending in the application.
- 4a) Of the above claim(s) 94-97, 101, 104, 105, 109 and 111-113 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 98-100, 102, 103, 106-108, 110 and 114-116 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 June 2009 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of the Claims

1. Claims 1-93 were originally filed on May 27, 2005.

The preliminary amendment received on June 4, 2008 canceled claims 1-93 and added new claims 94-113.

The amendment received on January 23, 2009 amended claims 100, 103, 107, and 111.

The amendment received on June 29, 2009 amended claims 98, 100, and 102 and added new claims 114-116.

Claims 94-116 are currently pending.

Claims 98-100, 102, 103, 106-108, 110, and 114-116 are currently under consideration.

Election/Restrictions

2. Applicants elected, with traverse, Group II (claims 98-110) in the reply filed on January 23, 2009. Claims 94-97 and 111-113 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

3. Applicants elected, without traverse, simultaneous addition as the species of when the candidate compound is added and fluorescent label as the species of label in the reply filed on January 23, 2009. Claims 101, 104-105, and 109 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim.

Priority

4. The present application claims status as a National Stage (371) of PCT/US04/20244 filed June 26, 2004 which claims benefit of provisional application 60/482,722 filed June 27, 2003.

Sequence Compliance

5. The present application is currently in compliance with the sequence rules.

Invention as Claimed

6. A method of identifying compounds having inhibitory activity against a bacterial strain comprising (a) preparing a cell-free reaction system comprising a bacterial RlmA protein or a rRNA binding domain thereof, a rRNA that binds said bacterial RlmA protein or the rRNA binding domain thereof, and a candidate compound, (b) detecting the extent of binding between the bacterial RlmA protein or the rRNA binding domain thereof and the rRNA wherein reduced binding between the bacterial RlmA protein or the rRNA binding domain thereof and the rRNA in the presence of the compound relative to a control is indicative of inhibitory activity of the compound against the bacterial strain, and variations thereof.

7. Please note: RlmA^I was previously known as RrmA and RlmA^{II} was previously known as TlrB.

Withdrawn Objections

8. The objection to the drawings regarding Figure 2C is withdrawn in view of the amendment received on June 29, 2009.
9. The objection to the abstract regarding various typographical and grammatical errors is withdrawn in view of the amendment received on June 29, 2009.
10. The objection to the disclosure regarding the first line of the specification is withdrawn in view of the amendment received on June 29, 2009.
11. The objection to the disclosure regarding the hyperlink is withdrawn in view of the amendment received on June 29, 2009.
12. The objection to claims 98-100, 102-103, 106-108, and 110 is withdrawn in view of the claim amendments received on June 29, 2009.

New Objections

Claim Objections

13. Claim 115 is objected to because of the following informalities: methyltransferase is misspelled in the claim. Appropriate correction is required.
14. Claim 116 is objected to because of the following informalities: *aeruginosa* is only partially italicized in the claim. Appropriate correction is required.

Withdrawn Rejections

15. The rejection of claims 98-100, 102-103, 106-108, and 110 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn upon further consideration.

16. The rejection of claims 98-100, 102-103, 106-108, and 110 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding antecedent basis (see below also) is withdrawn in view of the claim amendments received on June 29, 2009.

17. The rejection of claims 98-100, 102-103, 106-108, and 110 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments received on June 29, 2009.

18. The rejection of claim 98 under 35 U.S.C. 102(b) as being anticipated by Gustafsson et al., 1998, Identification of the rrmA Gene Encoding the 23S rRNA m¹G745 Methyltransferase in *Escherichia coli* and Characterization of an m¹G745-Deficient Mutant, Journal of Bacteriology, 180(2): 359-365 (provided by applicants in the IDS) is withdrawn in view of the claim amendments received on June 29, 2009.

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New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 98-100, 102, 103, 106-108, 110, and 114-116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection. Applicants pointed to paragraphs 26 and 53 and Figures 1A and 1B to provide support for the claim amendments received on June 29, 2009. However, support for a "cell-free" reaction system (see claims 98 and 114) was not found in paragraphs 26 or 53 or in Figures 1A or 1B. In addition, while there is support for RlmA derived from the various bacteria listed in new claim 116, there is not support for utilizing the various bacteria listed in new claim 116 in the presently claimed method (see the 112, second paragraph rejection below). Therefore, it is not clear at this time if the limitations of new claim 116 are new matter or not (clarification of the 112, second paragraph rejection will determine if the limitations are new matter or not).

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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22. Claim 114 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. For example, since dependent claim 114 incorporates all the limitations of independent claim 98, are method steps (a) and (b) of present claim 114 additional method steps (if so, please label as (c) and (d))? Is dependent claim 114 attempting to limit the reagents utilized in the method of claim 98 (the rRNA binding domain is not utilized, applicants may wish to make claim 114 independent or alter the language of claims 98 and/or 114)?

23. Claim 116 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. For example, independent claim 98 requires a "cell-free" reaction system. However, dependent claim 116 refers to various bacteria. It is not clear if the bacteria are utilized in the method or not.

24. Claim 116 recites the limitation "the bacteria" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Maintained Rejections

Claim Rejections - 35 USC § 112

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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26. Claims 98-100, 102-103, 106-108, 110, and 114-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 98 recites the limitation "the compound" in line 4 of method step b. There is insufficient antecedent basis for this limitation in the claim.

Arguments and Response

27. Applicants' arguments directed to the rejection under 35 USC 112, second paragraph (indefinite), for claims 98-100, 102-103, 106-108, 110, and 114-116 were considered but are not persuasive for the following reasons.

Applicants contend that the claim amendments received on June 29, 2009 negate the rejection.

Applicants' arguments are not convincing since the claim amendments received on June 29, 2009 did not correct line 4 of method step b.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

29. Claims 98-100, 102-103, 106-108, 110, and 116 are rejected under 35 U.S.C. 102(e) as being anticipated by Yuan U.S. Patent 6,610,504.

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For present claim 98, Yuan teaches methods of screening for inhibitors comprising (a) preparing a reaction system comprising a rRNA binding domain, a rRNA, and a candidate compound and (b) detecting if the candidate compound inhibits activity of the reaction system via altering binding between the rRNA binding domain and the rRNA via utilizing a control (please refer to the entire specification particularly the abstract; columns 2-4, 7, 9-10, 12, 13-17, 29-30, 32-38, 57-59; Table 2). In addition, Yuan teaches cell-free assays (see the entire specification particularly section c “Miniaturization” and the Examples).

For present claims 99 and 110, Yuan teaches high throughput assays and solid supports (please refer to the entire specification particularly columns 4, 7, 15, 30, 32-33, 36-37, 44).

For present claim 100, Yuan teaches reaction mixtures wherein all reagents are added simultaneously (please refer to the entire specification particularly column 30).

For present claims 102-103 and 106, Yuan teaches fluorescent labels (please refer to the entire specification particularly columns 34-36, 79).

For present claims 107-108, Yuan teaches fluorescence polarization anisotropy (please refer to the entire specification particularly columns 4, 36).

For present claim 116, Yuan teaches E. coli, etc. (please refer to the entire specification particularly Table 2).

Therefore, the presently claimed invention is anticipated by the teachings of Yuan.

Arguments and Response

30. Applicants’ arguments directed to the rejection under 35 USC 102 (e) as being anticipated by Yuan for claims 98-100, 102-103, 106-108, 110, and 116 were considered but are not persuasive for the following reasons.

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Applicants contend that Yuan only teaches assays for functional activity and not assays for physical binding between RlmA and rRNA. Applicants also contend that the functional assay taught by Yuan cannot be considered a reliable indirect measurement of the formation of a complex between rRNA and RlmA. Applicants state that the functional assay is a multistep process that includes binding of RlmA to rRNA, binding of S-adenosylmethionine to RlmA, catalysis of the methyl transfer, formation of S-adenosylhomocysteine, and release of S-adenosylhomocysteine.

Applicants' arguments are not convincing since the teachings of Yuan anticipate the methods of the instant claims. Yuan teaches various assays including functional activity, physical binding, etc. including assays that directly analyze nucleic acid-protein binding (please refer to the entire specification particularly columns 29-31, 57-63). Furthermore, it is noted that even in the functional assays wherein methylation is analyzed, binding is indirectly screened and is "indicative of inhibitory activity" (see MPEP § 2123, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." See *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) and *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968).).

Claim Rejections - 35 USC § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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32. Claims 98-100, 102-103, 106-108, 110, and 114-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan U.S. Patent 6,610,504 and Liu et al., 2002, Resistance to the macrolide antibiotic tylosin is conferred by single methylations at 23S rRNA nucleotides G748 and A2058 acting in synergy, PNAS, 99(23): 14658-14663 (provided by applicants in the IDS). For present claim 98, Yuan teaches methods of screening for methyltransferase (i.e. SAM methyltransferases preferred) inhibitors comprising (a) preparing a reaction system comprising a rRNA binding domain including rRNA methyltransferases, a rRNA, and a candidate compound and (b) detecting if the candidate compound inhibits activity of the reaction system via altering binding between the rRNA binding domain and the rRNA via utilizing a control (please refer to the entire specification particularly the abstract; columns 2-4, 7, 9-10, 12, 13-17, 29-30, 32-38, 57-59; Table 2). In addition, Yuan teaches cell-free assays (see the entire specification particularly section c “Miniaturization” and the Examples).

For present claims 99 and 110, Yuan teaches high throughput assays and solid supports (please refer to the entire specification particularly columns 4, 7, 15, 30, 32-33, 36-37, 44).

For present claim 100, Yuan teaches reaction mixtures wherein all reagents are added simultaneously (please refer to the entire specification particularly column 30).

For present claims 102-103 and 106, Yuan teaches fluorescent labels (please refer to the entire specification particularly columns 34-36, 79).

For present claims 107-108, Yuan teaches fluorescence polarization anisotropy (please refer to the entire specification particularly columns 4, 36).

For present claim 116, Yuan teaches E. coli, etc. (please refer to the entire specification particularly Table 2).

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However, Yuan does not specifically teach the rRNA methyltransferase RlmA.

For present claims 98 and 114-116, Liu et al. teach methods of screening comprising (a) providing a reaction system comprising RlmAI (i.e. rrmA) or RlmAII (i.e. tlrB or myrA), rRNA, and a candidate compound and (b) determining if the candidate compound alters bacterial growth compared to control (please refer to the entire reference particularly the abstract; pages 14659-14660; Tables 1-3).

The claims would have been obvious because the substitution of one known element (i.e. rRNA methyltransferase genus or specific species of trmA, trmD, etc. taught by Yuan in Table 2) for another (i.e. RlmA taught by Liu et al.) would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. inhibition of RlmA specific activity, discovery of antibiotics that are not resistant in the presence of RlmA). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Arguments and Response

33. Applicants' arguments directed to the rejection under 35 USC 103 (a) as being unpatentable over Yuan and Liu et al. for claims 98-100, 102-103, 106-108, 110, and 114-116 were considered but are not persuasive for the following reasons.

Applicants contend that Yuan only teaches assays for functional activity and not assays for physical binding between RlmA and rRNA. Applicants also contend that the functional assay taught by Yuan cannot be considered a reliable indirect measurement of the formation of a complex between rRNA and RlmA. Applicants state that the functional assay is a multistep process that includes binding of RlmA to rRNA, binding of S-adenosylmethionine to RlmA, catalysis of the methyl transfer, formation of S-adenosylhomocysteine, and release of S-

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adenosylhomocysteine. In addition, applicants contend that Liu et al. only discloses screening of compounds affecting bacterial growth in cell-based assays (i.e. not cell-free).

Applicants' arguments are not convincing since the teachings of Yuan and Liu et al. render the method of the instant claims *prima facie* obvious.

Yuan teaches various assays including functional activity, physical binding, etc. including assays that directly analyze nucleic acid-protein binding (please refer to the entire specification particularly columns 29-31, 57-63). Furthermore, it is noted that even in the functional assays wherein methylation is analyzed, binding is indirectly screened and is "indicative of inhibitory activity" (see MPEP § 2123, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." See *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) and *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968).). In addition, Yuan teaches cell-free assays (see the entire specification particularly section c "Miniaturization" and the Examples).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., reaction can not contain S-adenosylmethionine) are not recited in the rejected claim(s). Although the claims

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are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMBER D. STEELE whose telephone number is (571)272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Primary Examiner, Art Unit 1639

September 22, 2009